REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. AGENCY USE ONLY *(Leave blank)*

2. REPORT DATE
2007

3. REPORT TYPE AND DATES COVERED
Journal Article-Medicine & Science in Sports & Exer.

4. TITLE AND SUBTITLE
Military Applications of Hypoxic Training for High-Altitude Operations

5. FUNDING NUMBERS

6. AUTHOR(S)
S.R. Muza

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
Thermal and Mountain Medicine Division
U.S. Army Research Institute of Environmental Medicine
Natick, MA 01760-5007

8. PERFORMING ORGANIZATION REPORT NUMBER
M07-06

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
Same as #7 above

10. SPONSORING / MONITORING AGENCY REPORT NUMBER

11. SUPPLEMENTARY NOTES

12a. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for public release; distribution unlimited

12b. DISTRIBUTION CODE

13. ABSTRACT *(Maximum 200 words)*
Rapid deployment of unacclimatized Soldiers to high mountainous environments causes debilitating effects on operational capabilities (physical work performance), and force health (altitude sickness). Most of these altitude-induced debilitations can be prevented or ameliorated by a wide range of physiological responses collectively referred to as altitude acclimatization. Acclimatization to a target altitude can be induced by slow progressive ascents or continuous sojourns at intermediate altitudes. However, this "altitude residency" requirement reduces their utilization in rapid response military missions that exploit the air mobility capability of modern military forces to quickly deploy to an area of operations on short notice. A more recent approach to induce altitude acclimatization is the use of daily intermittent hypoxic exposures (IHE) in lieu of continuous residence at high altitudes. IHE treatments consist of three elements: 1) IHE simulated altitude (inspired oxygen partial pressure: PIO2), 2) IHE session duration, and 3) total number of IHE sessions over the treatment period. This paper reviews and summarizes the results of 25 published IHE studies. This review finds that an IHE altitude ?4,000 m, and daily exposure duration of at least 1.5 hours repeated over a week or more are required to have a high probability of developing altitude acclimatization. The efficacy of shorter duration (< 1.5 h) hypoxic exposures at ?4,000 m simulated altitudes, and longer exposures (> 4 h) at moderate altitudes (2500 - 3500 m) is not well documented. The predominate IHE-induced altitude acclimatization response appears to be increased arterial oxygen content through ventilatory acclimatization. Thus, IHE is a promising approach to provide the benefits of altitude acclimatization to low altitude-based Soldiers prior to their deployment to high mountainous regions.

14. SUBJECT TERMS
altitude acclimatization, acute mountain sickness, intermittent hypoxia, military operations

15. NUMBER OF PAGES
7

16. PRICE CODE

17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT
Unclassified	Unclassified	Unclassified	Unclassified

Military Applications of Hypoxic Training for High-Altitude Operations

STEPHEN R. MUZA

U.S. Army Research Institute of Environmental Medicine, Natick, MA

ABSTRACT

MUZA, S. R. Military Applications of Hypoxic Training for High-Altitude Operations. *Med. Sci. Sports Exerc.*, Vol. 39, No. 9, pp. 1625–1631, 2007. Rapid deployment of unacclimatized soldiers to high mountainous environments causes debilitating effects on operational capabilities (physical work performance), and force health (altitude sickness). Most of these altitude-induced debilitations can be prevented or ameliorated by a wide range of physiological responses collectively referred to as altitude acclimatization. Acclimatization to a target altitude can be induced by slow progressive ascents or continuous sojourns at intermediate altitudes. However, this "altitude residency" requirement reduces their utilization in rapid response military missions that exploit the air mobility capability of modern military forces to quickly deploy to an area of operations on short notice. A more recent approach to induce altitude acclimatization is the use of daily intermittent hypoxic exposures (IHE) in lieu of continuous residence at high altitudes. IHE treatments consist of three elements: 1) IHE simulated altitude (inspired oxygen partial pressure: PIO_2), 2) IHE session duration, and 3) total number of IHE sessions over the treatment period. This paper reviews and summarizes the results of 25 published IHE studies. This review finds that an IHE altitude ≥ 4000 m, and daily exposure duration of at least 1.5 h repeated over a week or more are required to have a high probability of developing altitude acclimatization. The efficacy of shorter duration (< 1.5 h) hypoxic exposures at ≥ 4000 m simulated altitudes, and longer exposures (> 4 h) at moderate altitudes (2500–3500 m) is not well documented. The predominate IHE-induced altitude acclimatization response appears to be increased arterial oxygen content through ventilatory acclimatization. Thus, IHE is a promising approach to provide the benefits of altitude acclimatization to low-altitude-based soldiers before their deployment to high mountainous regions. **Key Words:** ALTITUDE ACCLIMATIZATION, ACUTE MOUNTAIN SICKNESS, INTERMITTENT HYPOXIA, MILITARY OPERATIONS

BASIC SCIENCES

Modern military operations frequently require rapid deployment of personnel into extreme environments (heat, cold, altitude) with little or no time for physiological acclimation. However, rapid deployment of unacclimatized soldiers to high (> 1500 m) mountainous environments may cause debilitating effects on operational capabilities (i.e., physical work performance) and force health (i.e., altitude sickness).

All unacclimatized soldiers experience marked decreases in maximal and submaximal aerobic performance at elevations above 1500 m (8). With increasing altitude $\dot{V}O_{2max}$ decreases, thus the submaximal oxygen uptake for a given workload at altitude represents a greater percentage of the reduced $\dot{V}O_{2max}$. The practical implication is that tasks that require a fixed amount of exercise or work to be performed as quickly as possible (e.g., traveling from point A to B or unpacking a supply truck) must necessarily be conducted at a higher relative exercise intensity at altitude than at sea level.

In many individuals, the stress of the hypoxic environment causes physiological dysfunctions, which may be manifest in the form of several altitude illnesses, of which the most common is acute mountain sickness (AMS). AMS is a syndrome that is characterized by headache, anorexia, nausea, vomiting, insomnia, lassitude, and malaise (9). AMS susceptibility is greatest in unacclimatized lowlanders rapidly ascending above 2500 m and performing sustained physical work. Between 2000 and 3960 m, the incidence and severity of AMS in unacclimatized soldiers rapidly increases from about 20 to 70% (9). The symptoms of AMS appear within 4–24 h of exposure, and they typically resolve after 3–5 d as acclimatization to hypoxia is achieved. AMS is usually self-limited, but may progress into high-altitude cerebral edema (HACE) or high-altitude pulmonary edema (HAPE), both of which are potentially life threatening (9).

The natural countermeasure to the aforementioned altitude-induced physical performance decrements and AMS is altitude acclimatization. Lowlanders who continuously reside at high altitude develop a variety of physiological adaptations during altitude acclimatization. Two, in particular,

Address for correspondence: Stephen R. Muza, Ph.D., Thermal and Mountain Medicine Division, U.S. Army Research Institute of Environmental Medicine, Natick, MA 02053; E-mail: stephen.muza@us.army.mil.
Submitted for publication November 2006.
Accepted for publication May 2007.

0195-9131/07/3909-1625/0
MEDICINE & SCIENCE IN SPORTS & EXERCISE®

DOI: 10.1249/mss.0b013e3180de49fe

lessen the hypoxemia: increased ventilation and decreased plasma volume (i.e., hemoconcentration). Ventilatory acclimatization to altitude is characterized by a progressive increase in ventilation, arterial oxygen partial pressure (PaO_2) and oxygen saturation (SaO_2), and a drop of arterial carbon dioxide partial pressure ($PaCO_2$) along with normalization of arterial pH during the first 5–9 d of residence at high altitude (4). Concomitant with the increase in ventilation, the oxygen carrying capacity of the blood is increased by hemoconcentration resulting from reduction in plasma volume (19). The net result of the increased ventilation and hemoconcentration is a near normalization of arterial oxygen content after approximately 14 d of residence at high altitude. Further expansion of the blood oxygen carrying capacity is accomplished by the secretion of erythropoietin which causes an increase in red blood cell mass over three or more weeks residence at high altitude (3).

With continuous altitude residence the physiological strain of exercise is lessened, and exercise tolerance at altitude is improved compared to that initially on arrival (17). Likewise, the symptoms of AMS abate with acclimatization (9). For example, at 4300 m exercise performance measured by endurance at a fixed workload or time-trial increases by 25–60% during 8–16 d (7,17). Likewise, if individuals afflicted with AMS stop further ascent and rest at their current altitude, in approximately 80%, AMS symptoms resolve within 2–7 d (9) as acclimatization to hypoxia is achieved.

Depending on the altitude to which a previously unacclimatized lowlander has ascended, the time course for altitude acclimatization is 4–11 d (33). Consequently, above 1500 m, ascent rates that exceed the time course of acclimatization will increase the risk of developing altitude-induced debilitations (8,14). Current guidance recommends that above 2000 m, ascent should be limited to no more than 300–600 $m \cdot d^{-1}$, or after a rapid ascent of about 900 m, further ascent should be restricted for at least 3 d (12–14,33).

While staging and slow ascent protocols effectively induce acclimatization and reduce the incidence and severity of AMS, they are dependent on continuous residence at high altitudes to achieve these results. This ''altitude residency'' requirement reduces their utilization in rapid response military missions that exploit the air mobility capability of modern military forces to quickly deploy to an area of operations on short notice. A more recent approach to altitude acclimatization is the use of daily intermittent hypoxic exposures (IHE) in lieu of continuous residence at high altitudes. While the bulk of studies examining the potential beneficial effects of IHE treatments have focused on improving low-altitude physical performance (i.e., natural blood doping, etc.), a growing number have examined the ability of IHE treatments to induce altitude acclimatization. Recent studies (Tables 1–4) have demonstrated that IHE treatments can induce various degrees of altitude acclimatization in personnel residing at low altitudes (< 1000 m).

IHE treatments can be administered using either hypobaric hypoxia or normobaric hypoxia. In the former, hypoxia is induced by decreased barometric pressure either by ascending to higher elevations (such as in the live high–train low paradigm) or by simulated altitude exposure in a hypobaric chamber. Normobaric hypoxia is produced by nitrogen dilution of the inspired air in a small space (tent or room) or mask to lower the PIO_2 to a desired level (for purposes of comparison, throughout this review the level of hypoxia is presented as the equivalent altitude in meters no matter which method of inducing hypoxia is employed). Compared with hypobaric chambers, normobaric hypoxic rooms/tents are relatively inexpensive, and most importantly due to their light weight and small footprint can be shipped and set up to operate anywhere electrical power is

TABLE 1. Indices of ventilatory acclimation after intermittent hypoxic exposures (IHE).

IHE Daily Duration (h)	No. of IHE Sessions per Trial Period (d)	IHE Altitude (m)	IHT Time (%)	Outcome Test Altitude	Outcome Metric	Outcome Metric Response	Reference
0.5	24/28	2250 *H*	100	2250–3450 *H*	$e\dot{V}_E$	↔	(38)
0.5	24/28	3450 *H*	100	2250–3450 *H*	$e\dot{V}_E$	↔	(38)
0.5	18/42	3200 *N*	100	3200 *N*	$eSaO_2$	↑ 4%	(43)
0.75	25/35	2500 *H*	66	2500 *H*	$rPaO_2$, rHVR	↑ 10%, ↑ 41%	(29)
1.5	6/6	4500 *H*	0	4500 *H*	$rSaO_2$, rHVR	↑ 14%, ↑ 30%	(20)
1.5	6/6	4500 *H*	33	4500 *H*	$rSaO_2$, rHVR	↑ 7%, ↔	(20)
1.5	10/14	4500 *H*	33	SL	rHVR	↔	(21)
1.5	7/7	4500 *H*	0	4500 *H*	$r/eSaO_2$	↑ 7.5%	(23)
1.5	7/7	4500 *H*	0	SL	rHVR	↑ 62%	(25)
1.5	7/7	4500 *H*	0	SL	rHVR	↑ 69%	(24)
1.5	9/27	5500 *H*	0	5500 *H*	$rSaO_2$	↑ 30%	(37)
2	5/5	3800 *N*	0	3800 *N*	$rSaO_2$, rHVR	↔, ↑ 190%	(10)
2	12/12	3800 *N*	0	3800 *N*	$rSaO_2$, rHVR	↔, ↔	(10)
2	14/14	5000 *H*	0	5000 *H*	$eSaO_2$	↑ 9%	(34)
4	15/19	4300 *H*	25	4300 *H*	$r/eSaO_2$	↑ 6%	(1)
5	3/4	6000 *H*	0	8000 *H*	$rPaO_2$	↑ 5%	(32)
6–8	15/19	2650 *N*	0	2650 *N*	$sSaO_2$	↔	(26)
8	5/5	4300 *N*	0	4300 *N*	$sSaO_2$, $rPETCO_2$	↑ 3%, ↓ 10%	(28)
8	5/5	4500–8500 *H*	20	4500 *H*	$rPaO_2$, $rSaO_2$	↑ 12%, ↑ 4%	(39)
9	3/3	2650 *N*	0	2650 *N*, SL	rHVR	↑ 144%	(41)
16	28/28	2500 *H*	25	2500 *H*	$eSaO_2$	↑ 5%	(6)

Ventilatory acclimation indices assessed by increased $\dot{V}_E$, PAO_2, PaO_2, or SaO_2 at high altitude, or decreased $PACO_2$, $PaCO_2$ at high altitude or low altitude, or increased HVR measured during rest (r), exercise (e), or sleep (s). The magnitude of each outcome response is expressed as the percent change from baseline. ↔ no significant change. Altitudes are shown as hypobaric (*H*) or normobaric hypoxia (*N*) in equivalent meters above sea level. IHT time (%), duration of exercise training as a percentage of total daily IHE duration.

TABLE 2. Indices of hematological acclimatization after intermittent hypoxic exposure (IHE) treatments.

IHE Daily Duration (h)	No. of IHE Sessions per Trial Period (d)	IHE Altitude (m)	IHT Time (%)	Outcome Metric	Outcome Metric Response	References
0.5	24/28	2250–3450 *H*	100	Hb	↔	(38)
1.5	9/27	5500 *H*	0	Hb, RBC#, reticulocytes	↑ 13%, ↑ 7%, ↑ 200%	(37)
2	12/12	3800 *N*	0	Hb, Hct, reticulocytes	↔, ↔, ↑ 48%	(10)
2	14/14	5000 *H*	?	Hb	↔	(34)
3–5	9/9	4000–5500 *H*	20	Hb, Hct, RBC#, reticulocytes	↑ 16%, ↑ 7%, ↑ 150%	(36)
3–5	17/17	4000–5500 *H*	25	Hb, RBC#	↑ 9%, ↑ 11%	(5)
4	3/21	4000 *H*	80	Hb, Hct	↔	(42)
4	15/19	4300 *H*	25	Hb, Hct	↔	(2)
8	5/5	4500–8500 *H*	20	Hb, reticulocytes	↔, ↑ 44%	(39)
16	28/28	2500 *H*	25	RBC volume	↑ 8%	(6)

Hb, hemoglobin concentration; Hct, hematocrit; RBC#, red blood cell count. The magnitude of each outcome response is expressed as the percent change from baseline. ↔ no significant change. Altitudes are shown as hypobaric (*H*) or normobaric hypoxia (*N*) in equivalent meters above sea level. IHT time (%), duration of exercise training as a percentage of total daily IHE duration.

available. IHE treatments consist of three elements: the severity of the hypoxia (simulated altitude), the IHE session duration (here expressed in hours), and the number of IHE sessions (usually no more than one per day) over the trial period. In a hypothetical IHE procedure, personnel residing at a low-altitude base would participate in daily exposures to simulated altitude before deploying on a mission at high terrestrial elevations. In actual practice, the dose of IHE (altitude, exposure duration and number of sessions) could be titrated to the mission requirements, such as the operational target altitude, risk of developing AMS, and anticipated physical activity levels.

In assessing whether a particular IHE treatment is effective in producing altitude acclimatization, the appropriate outcomes must be measured. As previously reviewed, the magnitude of altitude acclimatization produced by conventional methods can be assessed (relative to the unacclimatized state) using appropriate physiological responses (e.g., increased ventilation, arterial oxygen saturation, hemoglobin or hematocrit, etc.) indicative of altitude acclimatization, and functional outcomes measured at high altitude, such as improved exercise endurance performance and decreased incidence and severity of AMS. Applying these accepted metrics of altitude acclimatization, and that the outcome must have been assessed at high altitude (real, or simulated) the IHE literature was reviewed. For inclusion in this review, each of the studies must have been published in a peer-reviewed journal, have tested individuals with no recent altitude acclimatization, and the study must have reported a statistical analysis of at least one of the outcome metrics presented above. For purposes of organization, the studies cited in each of the tables are sorted by the IHE session duration.

Before examining the specific outcomes from these studies, a general inspection of these studies presents several interesting observations. First, although not indicated in these tables, only a few of these studies were specifically conducted to study the efficacy of IHE to induce altitude acclimatization for subsequent high-altitude sojourns (1,5,32,36,39). Second, in the majority of the IHE studies, the outcome assessments were conducted within the first 24 h after the last IHE session, and in many studies the outcome assessments were made during the last IHE session. Thus, the ''persistence'' of the IHE-induced altitude acclimatization is not known. Third, only 5 of these 25 studies employed normobaric hypoxia for the IHE trials. Fourth, this review did not find a single study that used normobaric IHE, but then tested the outcome in hypobaric hypoxia. This latter observation is important for assessing the efficacy of normobaric IHE to acclimatize personnel for missions to high (hypobaric) terrestrial elevations. Although it is generally accepted that the major physiological responses (e.g., ventilatory, hematological) to high altitude are a function of the PIO_2 and not the absolute barometric pressure (18,27), two studies (30,35) have shown that AMS is significantly greater during hypobaric compared with normobaric hypoxic exposures, and that these differences may be due to pressure effects per se on

TABLE 3. Changes in maximum aerobic work performance and submaximal work endurance or time-trial performance at high altitudes after intermittent hypoxic exposure (IHE).

IHE Daily Duration (h)	No. of IHE sessions per Trial Period (d)	IHE Altitude (m)	IHT Time (%)	Outcome Test Altitude	Outcome Metric	Outcome Metric Response	References
0.5	18/42	3200 *N*	100	3200 *N*	$\dot{V}O_{2max}$	↔	(43)
0.5	24/28	2250 *H*	100	2250–3450 *H*	$\dot{V}O_{2max}$	↑ 8%	(38)
0.5	24/28	3450 *H*	100	2250–3450 *H*	$\dot{V}O_{2max}$	↑ 14%	(38)
0.5	30/42	3850 *N*	100	3850 *N*	$\dot{V}O_{2max}$	↑ 3–7%	(11)
0.5	18/42	3200 *N*	100	3200 *N*	TT	↔	(43)
1.5	7/7	4500 *H*	0	4500 *H*	$\dot{V}O_{2max}$	↔	(23)
2	20/28	2300 *H*	85	2300 *H*	W_{max}	↑ 15%	(40)
4	3/21	4000 *H*	80	4000 *H*	$\dot{V}O_{2max}$	↔	(42)
4	15/19	4300 *H*	25	4300 *H*	$\dot{V}O_{2max}$	↑ 18%	(2)
4	3/21	4000 *H*	80	2000 *H*	END	↑ 34%	(42)
4	15/19	4300 *H*	25	4300 *H*	TT	↑ 21%	(2)

Aerobic work performance assessed by increased $\dot{V}O_{2max}$, Wmax, submaximal endurance (END), or shorter time-trial (TT) duration at high altitude. The magnitude of each outcome response is expressed as the percent change from baseline. ↔ no significant change. Altitudes are shown as hypobaric (*H*) or normobaric hypoxia (*N*) in equivalent meters above sea level. IHT time (%), duration of exercise training as a percentage of total daily IHE duration.

TABLE 4. Changes in acute mountain sickness (AMS) symptom severity at high altitudes after intermittent hypoxic exposure (IHE).

IHE Daily Duration (h)	No. of IHE Sessions per Trial Period (d)	IHE Altitude (m)	IHT Time (%)	Outcome Test Altitude	Outcome Metric	AMS Symptom Severity	References
4	15/19	4300 *H*	25	4300 *H* [a]	LL AMS	↓ 80%	(1)
8	5/5	4300 *N*	0	4300 *N* [b]	LL AMS	↓ 86%	(28)

AMS assessed by symptom self-reports using the validated Lake Louise (LL) AMS questionnaire. The magnitude of each outcome response is expressed as the percent change from baseline. Altitudes are shown as hypobaric (*H*) or normobaric hypoxia (*N*) in equivalent meters above sea level. IHT time (%), duration of exercise training as a percentage of total daily IHE duration.

[a] Altitude exposure duration ≈ 30 h; [b] altitude exposure duration ≈ 8 h.

body fluid regulatory hormones (30). Thus, it remains to be determined whether normobaric IHE protocols are as effective as hypobaric IHE protocols for acclimatization to the natural hypobaric environment.

With these caveats acknowledged, inspection of the results summarized in Tables 1–4 clearly shows that across all outcome assessments, in 40 of 59 metrics, IHE demonstrated a beneficial altitude acclimatization response. It is also clear that the combinations of effective IHE session altitude, IHE session duration, and number of IHE sessions per trial period vary greatly. To aid in assessing the relative contribution of each of these IHE treatment elements, data from these IHE studies were qualitatively assessed to provide some insight regarding the relative contribution of each of these IHE treatment elements. For example, the IHE session altitude must be high enough to trigger the physiological adaptive responses. The lowest IHE session altitude is 2000 m, which is equivalent to a PIO_2 of 125 mm Hg. This altitude is also consistent with the previously recommended staging altitudes (12–14) and is an altitude at which significant (but not limiting) physical performance decrements (~15%) (8) and AMS (~25% incidence) (15) can occur. Higher IHE session altitudes seem to produce a proportionally greater physiological strain that may accelerate development of acclimatization. For example, there is evidence that for some individuals the threshold to produce adaptive responses is beyond 2500 (6), suggesting higher IHE session altitude exposures are necessary to ensure development of altitude acclimatization. For example, using indices of ventilatory acclimatization (Table 1), six of the eight negative outcomes occurred in IHE studies using a simulated altitude less than 4000 m. This observation suggests that IHE simulated altitudes greater than 4000 m are needed to have a high probability of developing ventilatory acclimatization.

In addition to the exposure altitude, the IHE session duration and frequency should also influence the development of altitude acclimatization. In this review, there are no published reports of studies that maintained the simulated altitude and frequency constant while only varying the daily exposure duration. Using the available data, visual inspection of Table 1 does not indicate any trend towards a larger ventilatory acclimatization response with increasing daily exposure time. To control for the effect of varying altitude, only studies using similar exposure altitudes were examined. Of the five IHE studies (1,20,23,28) conducted at 4300–4500 m that measured resting or exercise SaO_2, the daily IHE duration (range: 1.5–8 h) and number of exposures (5–15 d) did not seem to influence the magnitude of the observed SaO_2 increase. Thus, it seems that daily IHE-exposure durations of 1.5 h are as equally effective as 4–8 h at simulated altitudes of 4300 m or higher. Other observations include 1) the shortest IHE session durations were usually paired with a greater number of IHE sessions per trial period, and 2) the longest IHE session durations usually were administered overnight during sleep, and thus were paired with lower simulated altitudes. On the basis of these studies, to achieve a high probability of developing ventilatory acclimatization, we conclude that the IHE session altitude should be greater than 4000 m, and the exposure duration should be at least 1.5 h, repeated for a minimum of 5–6 d. However, the potential efficacy of shorter-duration (< 1.5 h) hypoxic exposures at ≥ 4000 m simulated altitudes, and longer exposures (> 4 h) at moderate altitudes (2500–3500 m) are not well documented and need further study.

As previously reviewed, in addition to ventilatory acclimatization in the early stages of continuous altitude exposure plasma volume reduction leads to significant increases in hemoglobin concentration, and over the course of several weeks increased erythropoiesis (3,19). These hematological adaptations increase arterial oxygen capacity and oxygen delivery. A review of the effects of IHE on inducing hematological adaptations to hypoxia is presented in Table 2. Inspection of these results demonstrates that hematological adaptations after IHE are far less certain than ventilatory adaptations. Only slightly more that half of the hematological outcome metrics observed some significant change consistent with increased oxygen carrying capacity, and there appeared to be no clear relationship between development of these hematological adaptations and the altitude, duration or frequency of IHE. The only measured increase in red blood cell volume was, in fact, a live high–train low paradigm in which the hypoxic exposures were 16 or more hours per day (6). Furthermore, as reported by Beidleman et al. (2) after IHE the magnitude of hemoconcentration measured over 24 h at 4300 m was not different from the unacclimatized state before IHE. The authors concluded that their IHE protocol did not enhance the subsequent acute hemoconcentration response to a subsequent continuous hypobaric hypoxic exposure. Thus, on the basis of these studies (Tables 1 and 2), ventilatory acclimatization seems to be the predominate mechanism to increase arterial oxygen content at high altitude after IHE.

Ultimately, the efficacy of IHE to induce altitude acclimatization is primarily determined not by the physiological adaptations, but rather by the physical performance and altitude sickness outcome metrics. Table 3 present studies of maximal aerobic work performance and submax endurance/time-trial performance performed at high altitudes after IHE. Maximal aerobic work performance (measured as $\dot{V}O_{2max}$ or W_{max}) was increased at high altitudes in five of the eight (63%) IHE studies. There seemed to be no significant relationship between improvements of maximal aerobic work performance and any of the IHE parameters (altitude, session duration, frequency, or duration of training during IHE). However, the observation that over half of the IHE studies demonstrated an improvement of maximal aerobic work performance at high altitude highlights a potential significant difference between IHE-induced verses continuous hypoxic exposure induced altitude acclimatization. In the latter, altitude acclimatization does not increase maximal aerobic work performance at high altitudes (8). Thus, IHE may have an advantage over continuous hypoxic exposure for enhancing physical work performance at high altitudes. There have been relatively few studies of either endurance or time-trial performance at high altitude after IHE. Of the three studies presented in Table 3, two reported improved performance. Both of these studies used similar IHE altitudes (> 4000 m) and daily exposure duration (4 h). Interestingly, one study used only one IHE exposure per week with positive results. This again demonstrates the need to perform controlled studies that only vary one of the IHE exposure parameters at a time to determine their relative contribution to a given acclimatization metric.

Review of this IHE literature was unable to determine whether exercise training during the IHE session improved subsequent aerobic work performance at high altitude to a greater extent than sedentary IHE exposures alone. Only one study (2) compared a group training in IHE to a sedentary group exposed to the same IHE. Although they observed no differences, the number of subjects in their study was very small. Thus, it remains to be determined whether physical training during IHE improves aerobic performance at high altitude more than sedentary exposure alone. There is reason to hypothesize that including physical training during IHE should augment aerobic performance at high altitudes. During continuous altitude (2300 m) exposure, subjects performing training during their altitude residence showed greater improvements in exercise performance than nontraining subjects (31). This finding supports the concept that to obtain the maximum physical work performance improvements at high altitude, one should include physical training at high altitude in their acclimatization program. A final consideration is identification of the ideal IHE training altitude. The degree of hypoxia must be sufficient to elicit a hypoxic response, but not too severe as to limit training intensity and risk the well-being of the subject during the training. Although little work has been done to identify the ideal IHE training altitude, based on their experience training athletes for competition at altitude, Hoppeler and Vogt (16) recommend a training altitude around 3000 m.

There may be a negative side effect of physical training at high altitude. Several studies by Katayama (20–22) have shown that when the subjects exercise trained for 0.5 h of an approximately 1.5 h of daily IHE, they did not increase their hypoxic ventilatory response, a measure of ventilatory acclimatization. Furthermore, Katayama has shown that exercise training at sea level depresses the hypoxic ventilatory response (20,21). These findings suggest that exercise training during relatively short daily IHE may impair ventilatory acclimatization. Thus, IHE procedures that include exercise training must be of sufficient daily duration to also provide a period of passive exposure to ensure development of ventilatory acclimatization. The best ratio of IHT-to-resting IHE duration has not been determined.

One of the least studied outcomes of IHE is its possible beneficial effects on reducing susceptibility to AMS during subsequent high-altitude sojourn. Presented in Table 4 are the results of the only two studies that have objectively assessed AMS after IHE. While these two laboratory-based studies (1,28) demonstrated a significant reduction in AMS incidence and severity after IHE, because the pre-IHE incidence and severity of AMS in both studies was relatively low it remains to be conclusively demonstrated whether IHE treatments can reduce susceptibility to altitude sickness in high risk conditions (rapid ascent with sustained physical activity at high altitude).

In summary, IHE is a promising approach to provide the benefits of altitude acclimatization to soldiers before their deployment to high mountainous regions. On the basis of the this review, it seems that an IHE exposure altitude greater than 4000 m and a daily exposure duration of at least 1.5 h repeated over a week or more are required to have a high probability of developing altitude acclimatization. The predominate IHE-induced altitude acclimatization response seems to be increased arterial oxygen content through ventilatory acclimatization. IHE does not appear to induce hemoconcentration through plasma volume reduction typically observed during continuous high-altitude exposures. Although numerous studies have demonstrated that daily IHE can induce altitude acclimatization in low-altitude (< 1500 m) residents, the vast majority of these studies lack systematic and quantifiable assessment of the outcome measures previously reviewed. Also, as noted, there has not been any study of the efficacy of normobaric IHE on improving physical work performance or decreasing AMS during a subsequent ascent to a hypobaric high-altitude environment. Finally, the design of future IHE studies must consider the limitations imposed by premission military preparations on the personnel's availability to participate in an IHE conditioning program. The minimal duration and frequency of the IHE sessions required to produce effective altitude acclimatization needs to be determined. Lastly, it remains to be determined how long after completing the last IHE session effective altitude acclimatization is retained with continued residence at low altitude.

The author would like to thank his colleagues, Drs. Allen Cymerman, Charles Fulco and Beth Beidleman for their support and assistance.

Approved for public release; distribution is unlimited.

The views, opinions and/or findings contained in this publication are those of the authors and should not be construed as an official Department of the Army position, policy or decision unless so designated by other documentation.

The investigators have adhered to the policies for protection of human subjects as prescribed in Army Regulation 70-25, and the research was conducted in adherence with the provisions of 45 CFR part 46.

REFERENCES

1. Beidleman, B. A., S. R. Muza, C. S. Fulco, et al. Intermittent altitude exposures reduce acute mountain sickness at 4300 M. *Clin. Sci. (Lond.)* 106:321–328, 2004.
2. Beidleman, B. A., S. R. Muza, C. S. Fulco, et al. Intermittent altitude exposures improve muscular performance at 4,300 m. *J. Appl. Physiol.* 95:1824–1832, 2003.
3. Berglund, B. High-altitude training. Aspects of haematological adaptation. *Sports Med.* 14:289–303, 1992.
4. Bisgard, G. E., and H. V. Forster. Ventilatory responses to acute and chronic hypoxia. In: *Handbook of Physiology Section 4: Environmental Physiology*, M. J. Fregly and C. M. Blatteis (Eds.). New York, NY: Oxford University Press, pp. 1207–1239, 1996.
5. Casas, M., H. Casas, T. Pages, et al. Intermittent hypobaric hypoxia induces altitude acclimation and improves the lactate threshold. *Aviat. Space Environ. Med.* 71:125–130, 2000.
6. Chapman, R. F., J. Stray-Gundersen, and B. D. Levine. Individual variation in response to altitude training. *J. Appl. Physiol.* 85: 1448–1456, 1998.
7. Fulco, C. S., K. W. Kambis, A. L. Friedlander, P. B. Rock, S. R. Muza, and A. Cymerman. Carbohydrate supplementation improves time-trial cycle performance during energy deficit at 4300 m altitude. *J. Appl. Physiol.* 99:867–876, 2005.
8. Fulco, C. S., P. B. Rock, and A. Cymerman. Maximal and submaximal exercise performance at altitude. *Aviat. Space Environ. Med.* 69:793–801, 1998.
9. Gallagher, S. A., and P. H. Hackett. High-altitude illness. *Emerg. Med. Clin. North Am.* 22:329–355, 2004.
10. Garcia, N., S. R. Hopkins, and F. L. Powell. Effects of intermittent hypoxia on the isocapnic hypoxic ventilatory response and erythropoiesis in humans. *Respir. Physiol.* 123:39–49, 2000.
11. Geiser, J., M. Vogt, R. Billeter, C. Zuleger, F. Belforti, and H. Hoppeler. Training high-living low: changes of aerobic performance and muscle structure with training at simulated altitude. *Int. J. Sports Med.* 22:579–585, 2001.
12. Hackett, P. H. Acute mountain sickness—the clinical approach. *Adv. Cardiol.* 27:6–10, 1980.
13. Hackett, P. H., D. Rennie, and H. D. Levine. The incidence, importance, and prophylaxis of acute mountain sickness. *Lancet* 2:1149–1154, 1976.
14. Hackett, P. H., and R. C. Roach. High-altitude illness. *N. Engl. J Med.* 345:107–114, 2001.
15. Honigman, B., M. K. Theis, J. Koziol-McLain, et al. Acute mountain sickness in a general tourist population at moderate altitudes. *Ann. Intern. Med.* 118:587–592, 1993.
16. Hoppeler, H., and M. Vogt. Hypoxia training for sea-level performance. Training high–living low. *Adv. Exp. Med. Biol.* 502:61–73, 2001.
17. Horstman, D. H., R. B. Weiskopf, and R. E. Jackson. Work capacity during 3-week sojourn at 4300 m; effects of relative polycythemia. *J. Appl. Physiol.* 35:385–390, 1980.
18. Howard, L. S., and P. A. Robbins. Ventilatory response to 8 h of isocapnic and poikilocapnic hypoxia in humans. *J. Appl. Physiol.* 78:1092–1097, 1995.
19. Hoyt, R. W., and A. Honig. Body fluids and energy metabolism at high altitude. In: *Handbook of Physiology Section 4: Environmental Physiology*, M. J. Fregly and C. M. Blatteis (Eds.). New York, NY: Oxford University Press, pp. 1277–1289, 1996.
20. Katayama, K., Y. Sato, K. Ishida, S. Mori, and M. Miyamura. The effects of intermittent exposure to hypoxia during endurance exercise training on the ventilatory responses to hypoxia and hypercapnia in humans. *Eur. J. Appl. Physiol. Occup. Physiol.* 78:189–194, 1998.
21. Katayama, K., Y. Sato, Y. Morotome, et al. Ventilatory chemosensitive adaptations to intermittent hypoxic exposure with endurance training and detraining. *J. Appl. Physiol.* 86:1805–1811, 1999.
22. Katayama, K., Y. Sato, Y. Morotome, et al. Cardiovascular response to hypoxia after endurance training at altitude and sea level and after detraining. *J. Appl. Physiol.* 88:1221–1227, 2000.
23. Katayama, K., Y. Sato, Y. Morotome, et al. Intermittent hypoxia increases ventilation and Sa(O2) during hypoxic exercise and hypoxic chemosensitivity. *J. Appl. Physiol.* 90:1431–1440, 2001.
24. Katayama, K., Y. Sato, N. Shima, et al. Enhanced chemosensitivity after intermittent hypoxic exposure does not affect exercise ventilation at sea level. *Eur. J. Appl. Physiol.* 87: 187–191, 2002.
25. Katayama, K., N. Shima, Y. Sato, et al. Effect of intermittent hypoxia on cardiovascular adaptations and response to progressive hypoxia in humans. *High Alt. Med. Biol.* 2:501–508, 2001.
26. Kinsman, T. A., C. J. Gore, A. G. Hahn, et al. Sleep in athletes undertaking protocols of exposure to nocturnal simulated altitude at 2650 m. *J. Sci. Med. Sport* 8:222–232, 2005.
27. Knaupp, W., S. Khilnani, J. Sherwood, S. Scharf, and H. Steinberg. Erythropoietin response to acute normobaric hypoxia in humans. *J. Appl. Physiol.* 73:837–840, 1992.
28. Kolb, J. C., P. N. Ainslie, K. Ide, and M. J. Poulin. Effects of five consecutive nocturnal hypoxic exposures on the cerebrovascular responses to acute hypoxia and hypercapnia in humans. *J. Appl. Physiol.* 96:1745–1754, 2004.
29. Levine, B. D., D. B. Friedman, K. Engfred, et al. The effect of normoxic or hypobaric hypoxic endurance training on the hypoxic ventilatory response. *Med. Sci. Sports Exerc.* 24:769–775, 1992.
30. Loeppky, J. A., R. C. Roach, D. Maes, et al. Role of hypobaria in fluid balance response to hypoxia. *High Alt. Med. Biol.* 6:60–71, 2005.
31. Mairbaurl, H., W. Schobersberger, E. Humpeler, W. Hasibeder, W. Fischer, and E. Raas. Beneficial effects of exercising at moderate altitude on red cell oxygen transport and on exercise performance. *Pflugers Arch.* 406:594–599, 1986.
32. Nagasaka, T., and T. Satake. Changes of pulmonary and cardiovascular functions in subjects confined intermittently in a low-pressure chamber for 3 consecutive days. *Fed. Proc.* 28:1312–1315, 1969.
33. Purkayastha, S. S., U. S. Ray, B. S. Arora, et al. Acclimatization at high altitude in gradual and acute induction. *J. Appl. Physiol.* 79:487–492, 1995.
34. Ricart, A., H. Casas, M. Casas, et al. Acclimatization near home? Early respiratory changes after short-term intermittent exposure to simulated altitude. *Wilderness Environ. Med.* 11:84–88, 2000.
35. Roach, R. C., J. A. Loeppky, and M. V. Icenogle. Acute mountain sickness: increased severity during simulated altitude compared with normobaric hypoxia. *J. Appl. Physiol.* 81:1908–1910, 1996.
36. Rodriguez, F. A., H. Casas, M. Casas, et al. Intermittent hypobaric hypoxia stimulates erythropoiesis and improves aerobic capacity. *Med. Sci. Sports Exerc.* 31:264–268, 1999.

37. Rodriguez, F. A., J. L. Ventura, M. Casas, et al. Erythropoietin acute reaction and haematological adaptations to short, intermittent hypobaric hypoxia. *Eur. J. Appl. Physiol.* 82:170–177, 2000.
38. Roskamm, H., F. Landry, L. Samek, M. Schlager, H. Weidemann, and H. Reindell. Effects of a standardized ergometer training program at three different altitudes. *J. Appl. Physiol.* 27:840–847, 1969.
39. Savourey, G., N. Garcia, Y. Besnard, A. Guinet, A. M. Hanniquet, and J. Bittel. Pre-adaptation, adaptation and de-adaptation to high altitude in humans: cardio-ventilatory and haematological changes. *Eur. J Appl. Physiol.* 73:529–535, 1996.
40. Terrados, N., J. Melichna, C. Sylven, E. Jansson, and L. Kaijser. Effects of training at simulated altitude on performance and muscle metabolic capacity in competitive road cyclists. *Eur. J. Appl. Physiol. Occup. Physiol.* 57:203–209, 1988.
41. Townsend, N. E., C. J. Gore, A. G. Hahn, et al. Living high-training low increases hypoxic ventilatory response of well-trained endurance athletes. *J. Appl. Physiol.* 93:1498–1505, 2002.
42. Vallier, J. M., P. Chateau, and C. Y. Guezennec. Effects of physical training in a hypobaric chamber on the physical performance of competitive triathletes. *Eur. J. Appl. Physiol. Occup. Physiol.* 73:471–478, 1996.
43. Ventura, N., H. Hoppeler, R. Seiler, A. Binggeli, P. Mullis, and M. Vogt. The response of trained athletes to six weeks of endurance training in hypoxia or normoxia. *Int. J. Sports Med.* 24:166–172, 2003.

BASIC SCIENCES